# A CONTRIBUTION

TO THE

# PATHOLOGY OF THE BLOOD

BEING

*AN ACCOUNT OF CERTAIN CRYSTALLINE CHANGES OCCURRING IN THE HÆMOGLOBIN AFTER WITHDRAWAL FROM THE BODY, IN THE SUBJECTS OF CERTAIN DISEASES, ESPECIALLY THOSE OF SEPTIC ORIGIN*

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# THE

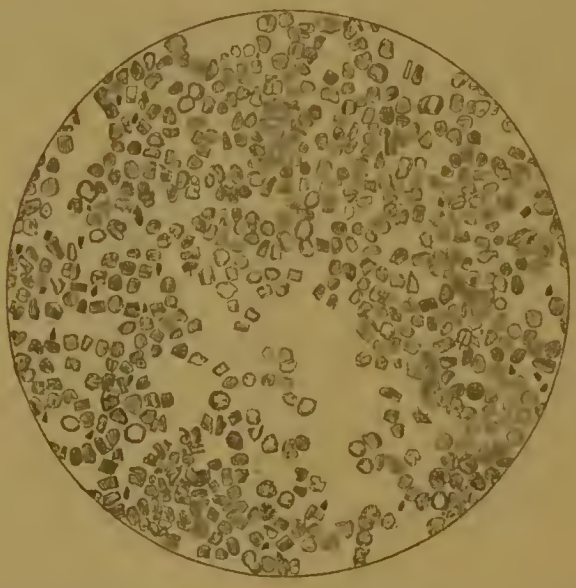
# PATHOLOGY OF THE BLOOD.

I MAKE no apology for bringing forward again the well-worn subject of crystallisation of the hæmoglobin of the red blood corpuscles; for I think, when viewed in the light about to be described, it is capable of suggesting many useful hints towards the better understanding of the pathology of many diseases, especially those which are associated with the septic processes.

If a drop of normal human blood be drawn from the finger, placed on a slide, and covered with a cover glass, no crystallisation of the hæmoglobin occurs. A ring or cake of dried serum forms around the edge of the cover glass, keeping the blood fluid within for many days; and although some changes occur, such as partial exudation of the hæmoglobin into the serum, there is no crystallisation of the hæmoglobin either in the serum or corpuscles. This is true of the blood of many of the mammals under like conditions —*i.e.*, the blood of the ox, sheep, dog, cat, mole, rabbit, and guinea-pig: and also in the nucleated blood of birds, frogs, toads, and newts. On the other hand, the blood of the apparently healthy mouse, both wild and tame varieties, shows, under the same conditions, well-marked crystallisation of its hæmoglobin, both in corpuscles and serum, in from twenty to thirty hours. Between these two extremes

are many stages, the blood of different animals varying greatly in its tendency to crystallise when withdrawn from the body, that of the same animal varying also according to the healthy or diseased condition it may be in at the time. It is to this crystalline change which human blood undergoes when withdrawn from the body in certain diseases that I wish to draw attention, and especially in those diseases which

Fig. 1.



Normal human blood to which has been added a drop of putrid serum: after standing on slide twenty-four hours. Shows early stage of crystallisation in septic blood, chiefly in red corpuscles. The ink dots (·) are placed near the corpuscles which show the change best—namely, the ridged, barred appearance, or the flat square plate or crystal form. (From micro-photograph taken with a $\frac{1}{5}$ objective and No. 1 ocular.)

are associated with the presence in the body of the pathogenic organisms.

At the outset, I would have it clearly understood, that what I maintain, and what I hope to prove, is, not that the blood crystallises in the body in the subjects of septic diseases, but that in certain animals, and in man, under certain conditions of disease, the blood, after withdrawal from the body,

shows under the microscope a tendency for its hæmoglobin to undergo exudation and crystallisation, in a period of time varying from twelve hours to several days. Neither do I wish to claim for this phenomenon more importance than it deserves; but value it rather from the way in which, though itself a post-mortem change, it enables us to group together certain diseased conditions, and in these remarks I desire to

Fig. 2.

Normal human blood to which has been added a drop of putrid serum: after standing two days. Shows later stage of crystallisation which has occurred in the form of large plates in the hæmoglobin dissolved in the serum. (From a micro-photograph, same as fig. 1.)

point out the various diseases in which this crystalline change occurs.

In the first place, as these crystals are somewhat easily overlooked, it may be well to give an example and describe the actual appearances under the microscope. If a drop of blood be taken from the cleansed finger of any patient who is suffering severely from absorption of the products of putrefaction either in a wound or elsewhere, and if such a

drop of blood be placed between a slide and cover glass and allowed to remain at the ordinary temperature of the room (60° F.), it will be found that, though it may appear quite normal at the time of withdrawal, after a time varying from twenty to thirty hours, the specimen will show the following changes :—First, the exudation of the hæmoglobin out of the corpuscles into the serum in an area round the margin of the cover glass is in excess of the exudation in normal blood, and gives the serum a marked yellow tinge. Secondly, in a zone just inside this ring or area, the corpuscles have lost their spherical or disc-like shape, and have many of them become single, or several crystals of hæmoglobin, and show the prismatic or needle shape peculiar to those crystals; while in some few corpuscles the inside of the corpuscle has apparently crystallised, and the little bars or needles can be plainly seen inside and apparently distinct from the enclosing stroma. Further, in a marked case the crystallisation will have proceeded further, and have occurred in the form of long parallelograms or needles in the area of exudation mentioned above. In fact, the amount of exudation and the fulness of crystallisation are in proportion to the severity of the symptoms—that is, to the amount of poison absorbed. In a very slight case there is no apparent change; in one in which absorption is more complete or prolonged over a longer time there is slight excess of exudation with crystallisation in a few scattered corpuscles; in a fatal case the whole slide may appear studded with crystals. (See Figs. 1 and 2.) Now since this change does not show itself while the blood is still in the circulation, we can only call it a tendency existing in the circulating blood of patients who are the subjects of certain diseases to undergo, after withdrawal from the body, a peculiar crystalline change, a tendency which is not so shown by the blood of healthy persons. For several years I have examined the blood of many hundreds of patients in this simple way with reference only, or chiefly, to this point of crystallisation, noting down what occurred and the condition of the patient. I propose firstly

to give in an abstract form, the result of this examination, grouping the cases under the several heads of the different diseases; and then to offer some remarks on the nature of the change that the blood undergoes.

*Sapræmia or Septic Intoxication.*—In this affection the symptoms—rigors, high temperature, sickness, diarrhœa, headache, or delirium—are due to the presence in the circulation of an unorganised substance, the product of decomposition, and associated with the life-history of the organisms of putrefaction, the poison itself being called by various names—sepsin, zymin, &c. In severe cases the crystalline change is well marked. It varies, moreover, in direct proportion to the amount of poison absorbed, and to the interval elapsing between its introduction and the withdrawal and examination of the drop of blood. The following case illustrates these points:—

A patient was suffering from decomposition of a retained placenta, having a temperature of 106° on the second day after delivery, a pulse of 150, rigors, delirium, pain in the bones, and diarrhœa. The blood at this time, examined by Koch's method, showed no organisms whatever, but after remaining on the slide sixteen hours, marked crystallisation of the red corpuscles could be seen. The placenta was removed under $CH.Cl_3$, and the uterus thoroughly washed out with carbolic acid lotion. On the following morning—that is, in about twenty hours after the removal of the placenta—the temperature was normal and the pulse 100, the patient being almost convalescent. The blood now showed no tendency to crystallise at all, proving that, the source of the poison having been removed, and that already in the circulation having been excreted or destroyed, the blood had regained its normal condition in less than twenty-four hours. But, further, in two days' time slight decomposition again occurred in the uterine discharge; the temperature again rose to 102°, and the crystallisation reappeared, again to disappear on a further irrigation of the uterus.

In many cases of a like kind this tendency to crystallisa-

tion of the hæmoglobin has coincided in time with marked exacerbations of symptoms of septic absorption—appearing, for instance, shortly after the occurrence of rigors or rises of temperature, and disappearing as these subside.

But it must not be supposed that the absorption of a small amount of poison will produce this change in the whole volume of the blood. I have not found it in cases of wounds or abscess where the rise of temperature and the other symptoms of absorption have been only slight; in fact, it seems as though considerable and repeated doses of sepsin are required to change the whole blood in the body sufficiently to produce the tendency to crystallisation: whether this be owing to rapid excretion of the poison by the kidneys, or to some resisting power on the part of the corpuscles, is doubtful. It is, of course, also well known that the rate of absorption of sepsin depends somewhat on the tension in the wound or site of its production. This fact is also shown in another way by this crystallisation described in the following case:—

The blood was examined from the finger of a patient with a feculent abscess in a neglected and inflamed hernial sac. It showed marked crystallisation in forty-eight hours. A free incision was made, and the pus let out. Sixty hours afterwards, the tension having disappeared, although the cavity continued to discharge a quantity of most offensive pus, the crystallisation could no longer be detected.

*The Septic Infective Diseases: Septicæmia and Pyæmia.*—I have examined the blood repeatedly in many cases of septicæmia and pyæmia—in cases which have and in those which have not been accompanied with abscesses in the internal organs, with suppuration of joints, and with secondary localised inflammation of the connective tissues. The crystalline tendency does not seem so constant or in such direct proportion to the severity of the symptoms at the time as in the case of sapræmia or septic intoxication, although it is present in most cases of septicæmia, and in nearly all fatal cases towards the end of the disease. It varies, too, in

the extent of the crystallisation and in the length of time the blood must stand on the slide after withdrawal before it appears, from day to day of the illness, and seems to have more connexion with the amount of poison absorbed at each separate septic focus than with the number or position of the abscesses. It appears, in fact, to depend not so much on the presence of the organisms in the blood as on the chemical products of their growth, and this view will receive further confirmation when we speak of anthrax.

*Erysipelas and Erysipelatous Inflammation of Cellular Tissue.*—In slight cases of this affection, where the local affection is not very extensive and the constitutional symptoms slight, the general blood, or that from the general circulation, shows no change. When, however, there is marked constitutional disturbance, the crystallisation appears in from twenty-four to forty-eight hours after withdrawal. But it was in the case of erysipelas that a difference was first noticed according to the site from which the blood was taken. Thus in the case of a man with marked erysipelatous cellulitis of hand and forearm without suppuration, the temperature being 104°, blood taken from the margin of the inflamed area crystallised fully in twenty-four hours, whereas a drop taken from the finger of the other hand only did so very partially after forty-eight hours. Also in a case of so-called "perambulating" erysipelas, in which the erysipelatous wave started from the breast and travelled over the greater part of the body, blood taken from the red inflammatory area about four inches wide crystallised well, while that taken from the healthy skin in front of the wave and from the tissue which had recovered after the wave had passed over it, showed little or no change. Thus we see that blood taken from a part of the body which is the site of an inflammation of an infective character shows a tendency to undergo crystalline degeneration, whereas the general blood of the body in such a case only does so after long and repeated constitutional infection. We must remember not only that the poison, whatever it be, is manufactured at this area, but that in addition, owing to

the extreme local vascular congestion, the blood is more or less stagnant here and lies long in contact with the inflamed tissues, and perhaps also with the organisms themselves; but this point will receive further consideration later on. It is sufficient here to suggest that, owing, perhaps, to rapid excretion, the poison only reaches in extreme cases a sufficient degree of concentration in the general circulation to produce this change in the whole volume of the blood. Whether the red corpuscles so damaged at the inflamed area recover on reaching the general circulation, or, as is more probable, undergo speedy disintegration in the liver and elsewhere, cannot yet be known; for not having the crystalline mark upon them while in the circulation, but only having been sufficiently injured to render them liable to show this change after withdrawal from the body, we cannot by this sign alone follow out their individual life histories. The anæmia and well-known rapid destruction of red corpuscles in the subjects of infective disease seem to support the latter view.

*Facial or so-called Idiopathic Erysipelas.*—In this variety, which also probably depends on infection through an unrecognised channel, the local affection is in most cases too limited to produce any general crystalline change.

*Diphtheria.*—This, like erysipelas, of course occurs in the two forms of wound infection, and the more frequent primary throat manifestation. I have examined the blood in many cases of the latter variety at all stages of the disease. The general crystalline tendency is not constant; if present it only occurs after the blood has remained on the slide from forty-eight hours to three or four days, and appears to bear some slight relation to the amount of constitutional infection, and very little to the local symptoms.

*Typhoid Fever.*—In all the uncomplicated cases of typhoid in which I have examined the blood—that is, cases arising in previously healthy persons, and uncomplicated with pneumonia, bedsores, abscesses, &c.—the crystalline blood change has never been detected. This is somewhat remarkable

when we remember that typhoid fever, like diphtheria and erysipelas, is a specific disease having a local manifestation in the intestines and constitutional effects, as seen in the rash, &c.; in this it resembles measles, scarlet fever, and small-pox, and it is interesting to note that, as in typhoid fever, so too the crystalline change is also absent in uncomplicated cases of *measles*, *scarlet fever*, and *small-pox*. *Typhus* I have not had an opportunity of examining. With regard to this latter group of diseases—diphtheria, typhoid, measles, and scarlet fever,—there are one or two interesting points which need further remark. They are more or less protective (that is, one attack confers immunity from a second) in a gradually increasing degree as we ascend the series: diphtheria least so; scarlet fever most so. Also diphtheria is perhaps the most local, and scarlet fever the most general or constitutional, in its manifestation. And, as if to correspond to this, diphtheria at one end of the series shows the crystalline blood change slightly, while it is absent in the other diseases. What is the exact meaning of this association we are not yet able to say.

*Anthrax, or Splenic Fever.*—This is, perhaps, the one example of a disease having an infective origin of which the pathology or life-history is fully known. First, in animals. In guinea-pigs, although the blood readily crystallises when treated in certain ways, it never does so when normal blood is placed on a slide in the manner described above; it does, however, crystallise on the slide if the animal be suffering from, for instance, a septic peritonitis, thus showing that the change is a test of some value in the case of these animals. A guinea-pig was inoculated subcutaneously with anthrax spores; in forty-eight hours it died, with marked symptoms of splenic fever. The blood examined at various stages of the disease was crowded with the bacilli, but showed no tendency to crystallise on the slide, either in the corpuscles or in the hæmoglobin that had exuded into the serum.

In the case of a veterinary surgeon who became inoculated while making a post-mortem on a cow, dead of splenic

fever, a well-marked characteristic malignant pustule appeared at the site of inoculation on the wrist. Examination of the discharge from this showed great numbers of the bacillus anthracis; the patient recovered after energetic injection round the pustule of pure carbolic acid. The general blood was examined before and during treatment; no bacilli were detected in it, and it never showed any crystalline tendency.

This was a case of so-called external anthrax or malignant pustule, in which the constitutional infection was very slight, and the influence of the organisms, or the absorption of poison at the site of inoculation, insufficient to produce a crystalline change in the whole volume of the blood. A distinction must be drawn between these cases and those of internal anthrax, in which the spores are received into the lungs; in these cases the constitutional effects appear to be more marked, and I have not been able to examine the blood in them. Judging, however, from the facts in animals, it would seem that anthrax ought really to be looked upon as a mycosis; that death is brought about by the invasion and plugging of the capillaries and lymphatics of the host by the thousands of bacilli, and not by the manufacture of any chemical poison, and this view receives some confirmation from the absence of the crystalline change in the blood in this disease.

*Pneumonia.*—The relationship between this disease and the presence of the organisms first described by Friedländer is now fairly well established. Whatever be the real relationship, however, whether the high temperature, &c., is the result of absorption of chemical products in the affected lung or due to other causes we do not know. In these acute cases the crystalline tendency is not at all constant, it was absent in a well-marked case in a boy with a temperature of 106°, and it only appears in fatal cases just before death or in long-continuing cases attended with breaking down of lung tissue. In the absence of further evidence, I think another cause besides septic absorption will be found to

explain the high temperature and constitutional symptoms, and I think the absence of the crystalline change points to this suggestion.

*Ague.*—I have examined the blood in several well-marked cases of ague in the pyrexial and following stages, and have not noticed any alteration of the corpuscles in the direction of crystallisation. Although ague is known to be caused by the presence of organisms in the system, we do not yet know the pathology of its latency and periodicity. If again the symptoms are due to absorption of chemical products, this is not sufficient in amount, or prolonged enough in time, to affect the whole volume of the blood.

*Phthisis.*—In this disease the crystalline tendency can generally be detected towards the end of fatal cases. In some acute cases it is, however, absent.

*General Tuberculosis.*—Two cases were examined, and no change detected.

*Cancrum Oris.*—Blood taken from the finger in a well-marked case of this emphatically infective process showed marked crystallisation in twenty-four hours.

Reviewing, then, this list of so-called infective diseases in which the blood has been examined, we find that the crystalline tendency is most marked in those diseases in which there is commonly the greatest evidence of absorption of chemical products; these are sapræmia, septicæmia, and pyæmia, erysipelas, cancrum oris, and advanced cases of phthisis. In the others it is inconstant or absent, and, as has been pointed out in the case of anthrax, this absence may suggest the possibility of the constitutional symptoms in these cases being due not merely to chemical absorption, but to some other as yet unknown factor or factors; this applies to such diseases as typhoid, pneumonia, scarlet fever, measles, &c. If we allow ourselves to speculate a little further on a question regarding which the evidence is at present very incomplete—if, for instance, we regard the immunity from subsequent attack conferred by one attack of many of these diseases, to be due to the fact, that the products or substances

evolved and circulating during the first attack have so acted on and changed the blood and tissues as to render them proof against further invasion by the same organisms—then, judging from the foregoing observations, it would appear that it is not the absorption and circulation of the highly differentiated protective product which produces in the blood this crystalline change, for it is absent in scarlet fever, measles, &c.; but that the less differentiated non-protective, simple product of putrefaction does so to a marked extent, as in sapræmia, &c., and this points to a marked difference in the products produced by the life and growth of different organisms.

We have now to consider the condition of the blood in those diseases, or rather aggregation of symptoms, associated with the presence in the blood or tissues of substances or chemical products not owing their origin to the life-history of micro-organisms. These conditions fall into two divisions: one in which the substance or poison is introduced from outside, as in the case of a patient saturated with ether; and another, in which the poison is produced in the body by disturbed or perverted metabolism and nutrition, as in the case of jaundice or uræmia. Now, as, indeed, we should expect from previous considerations, we find that, taken as a whole, the crystalline tendency is absent in all these cases.

Thus, in the first division, it is absent in the blood of patients who have been long under the influence of ether or chloroform. As a rule, it is absent in cases of opium poisoning. In one fatal case, however, slight crystallisation appeared after the blood had remained on the slide for forty-eight hours, and in this case the man had been in a state of complete coma or semi-asphyxia for twelve hours previously.

The second division will next be considered.

*Rheumatic Fever.*—The crystalline tendency is absent even in well-marked cases, with a temperature of from 101° to 104°. In one case of hyperpyrexia, however, in a syphilitic subject, in which the temperature rapidly rose from 99°

to 107°, it was interesting to note that at noon, the temperature being 107°, a drop of blood showed the crystalline change well after standing fifteen hours, whereas at 9 P.M., after energetic treatment with the ice pack, when the temperature gradually fell to and remained at 99°, a drop of blood only showed a very slight crystalline change after standing forty-eight hours; and two days later, the temperature still being 99°, no change could be detected even after standing two or three days. The only explanation of the presence of the crystalline change in this case of extreme pyrexia is that it occurred in a patient who was suffering at the time from paraplegia, due to syphilitic disease of the cord, and the sudden rise of temperature may have been due to further nerve influence, and not to chemical poisoning.

*Rheumatoid Arthritis.*—The crystalline tendency is absent in these chronic cases.

*Uræmia and Uræmic Coma.*—I have examined the blood in many cases of Bright's disease terminating fatally in coma or convulsions, and have never detected the crystalline tendency. Here the evidence is strong that the symptoms are due to some partially oxidised products of tissue change circulating in the blood, and the absence of crystallisation is worthy of notice.

*Diabetes.*—The blood in two cases of ordinary diabetes in which large quantities of sugar were passed daily showed no change. In two cases of diabetic coma or acetonæmia, fatal in from thirty to thirty-six hours, very slight crystallisation occurred after the blood had remained five days, and in another case of diabetic coma it was absent.

*Jaundice.*—We are only dealing here with jaundice as a certain symptom or condition of the system, due to the retention of a certain substance or substances, and not with reference to the disease producing it. In simple cases of jaundice, due, for instance, to catarrhal obstruction of the duct, I have never detected any crystalline change in the blood; on the contrary, the presence of bile salts in the blood seems to lessen the usual amount of exudation of the

hæmoglobin out of the corpuscles into the serum after withdrawal.

We may assume, therefore, from these facts, that the presence of chemical substances in the blood, which, like sugar in diabetes, or the nitrogenous bodies in uræmia, or the supposed lactic acid in rheumatic fever, or the bile salts in jaundice, are not formed by the growth of vegetable micro-organisms, is not in itself sufficient to produce this crystalline change in the hæmoglobin.

The following diseases are due to pathological changes in the blood or in certain organs not as yet demonstrated to be due to micro-organisms:—

*Anæmia.*—This is the condition in which, above all others, we should anxiously look for this crystalline change. It is, of course, however, necessary to distinguish carefully between the different diseases included under this name. In idiopathic anæmia or chlorosis, so common in young women, the blood has been examined in severe cases, and no crystalline tendency detected. This disease being probably due to a defective formation and supply of red corpuscles, it is interesting to know that those corpuscles which are in circulation have not that peculiar tendency to degeneration which leads them to crystallise after withdrawal from the body.

*Anæmia from Hæmorrhage.*—Here, too, there is no crystalline change; the corpuscles which remain appear healthy.

*Pernicious Anæmia.*—Four well-marked cases of this disease were examined repeatedly, and they present some interesting points of contrast. In two cases the blood contained only 50 per cent., or only half the normal numbers of red corpuscles, and these were badly shaped, and 23 per cent. and 50 per cent. respectively of the normal amount of hæmoglobin. Both patients had been ill for a long time, and had received no benefit from taking iron. Both recovered after taking arsenic for about two months, and in both cases the temperature was normal throughout. In neither case was any crystallisation detected in the blood.

In two other cases, one a girl aged sixteen, and one a man aged thirty-six, the symptoms were alike, but differed from those in the last two cases. In both there was at times sickness; both had relapses, relieved by arsenic, made worse by iron. In the man's case, he had an illness of the same kind a year previously, for which he took arsenic. He died eventually three months after leaving the hospital, probably from the same disease. The girl ultimately recovered. In both cases the temperature was constantly above normal, and occasionally ran up to 102° and 103°. In both there was the crystalline change in the blood; this disappeared in the girl's case as convalescence came on. In the man's case, a marked relationship existed between the amount of crystallisation of the blood and the amount of arsenic taken. Thus, it was found that after the arsenic had been taken for one week there was only slight crystallisation after the blood had stood five or six days, and eventually none at all. Whereas, if the arsenic were discontinued for some days, crystallisation reappeared after the blood had stood from twenty-four to forty-eight hours, and this association was repeatedly tested. These facts point to the suggestion that cases of pernicious anæmia are not all alike in their pathology; they differ in the important respect of temperature and crystalline degeneration in the blood-corpuscles. Moreover, cases in which these latter symptoms exist are more severe, and seem to have some of the appearances seen in cases of septic poisoning. The poverty of red corpuscles in this disease appears, according to recent researches (Hunter, Radcliffe, Oliver, &c.), to be due to an excessive destruction of these bodies in the liver, and perhaps in other organs; whether this is due to the agency of micro-organisms, or to a peculiar action of the hepatic cells, is not settled, and the arsenic may either act on the red corpuscles, or, as is more probable, on the liver cells themselves. It is also interesting to note that in one case the patient had previously suffered from jaundice. What the real difference is, if any exists, in intimate pathology between these two groups of cases, cannot be at present

demonstrated; it may be one only of degree of destruction of red corpuscles; but from our previous knowledge of the conditions under which crystallisation occurs in the blood, we should have been led to expect the presence in the blood in the latter group of cases of some poison or ferment associated with the growth of micro-organisms.*

*Addison's Disease.*—In two well-marked examples of this disease the blood was found to crystallise in from twenty-four to forty-eight hours after withdrawal, and the change was more marked the more severe the anæmia and debility—the nearer, in fact, to the fatal termination. It is, of course, well known that the blood is much changed in Addison's disease, the red corpuscles being diminished in number and misshapen; and now we see that, in addition, there is a tendency for its hæmoglobin to crystallise. The cause of this change, like that of the bronzing of the skin and the anæmia, is unknown, but may very probably be closely associated with these, perhaps having with them one common cause. It is, however, interesting to note that, as in the case of pernicious anæmia, the crystalline change bears some direct relation to the temperature, which varies irregularly in this disease.

*Splenic Leucocythæmia.*—It was the well-marked manner in which crystallisation occurred in the blood of persons suffering from this disease that first drew my attention to this subject. Indeed, it has been noticed by previous observers that after death the hæmoglobin readily crystallises in the blood of such patients. The crystals appear on the slide not only in the red corpuscles, but also in the form of large plates in the exuded hæmoglobin. Now, at once it is right to state, that there is evidence to show that the crystallisation is due to the presence in the blood of the leucocytes in large quantities and not to any primary change or degeneration in the red corpuscles. This point

* It is right to state that this was written in 1886, before the appearance of Dr. Copeman's article in THE LANCET of May 28th, 1887, on the Blood in Pernicious Anæmia.

will be discussed later, but this statement applies to cases in which the spleen is the organ solely or chiefly enlarged, and in which there is marked leucocythæmia; and it receives confirmation from the fact that in well-marked cases of Hodgkin's disease, in which the lymphatic glands may be enormously enlarged, but in which there is no marked excess of leucocytes in the circulation, crystallisation does not occur.

*Tumours or New Growths.*—For the purpose of this inquiry cases of tumour or new growth must be classified not according to their embryonic or histological characters, but may best be divided into two large divisions. 1. Cases in which the new growth is very vascular, rapidly growing, and situated in parts where rapid infiltration of surrounding tissues can occur, as in the case of internal organs, especially the liver. This group will include such forms as the soft round-celled sarcomata and the encephaloid carcinomata. 2. Cases in which the new growth is only moderately vascular, slowly growing, and more or less defined or limited in outline. This will include the non-malignant forms, and such cases of malignant disease as epithelioma, scirrhus, &c. In viewing tumours, moreover, in their relation to this blood change, we must exclude cases in which there is any possibility of septic poisoning by ulceration or peritonitis, &c., and also all cases in which there is a marked increase in the number of leucocytes in the blood, since we have reason to believe that, as in the case of splenic leucocythæmia, these bodies are capable of themselves producing this change. Further, the blood examined must be drawn from the finger or some convenient spot away from the tumour, for—and this point is very important—if a drop of blood be obtained by a hollow needle directly from a rapidly growing vascular new growth, and placed on a slide, it will of course contain numbers of cells and tissue elements from the tumour itself. Now such blood so treated and allowed to remain will show the crystalline change well in from twenty-four to forty-eight hours. In fact, the cells of the neoplasm seem to act

in contact with the red corpuscles, in the same way as the leucocytes in splenic leucocythæmia. Bearing these conditions in mind, I have found that in several cases included in Group 1, one a case of encephaloid of the liver, and one of lympho-sarcoma of the mesenteric glands, the crystalline change exists. Further, such cases in the course of the disease show at times irregular rises of temperature, reaching it may be 100° or 101°, and lasting perhaps a few days, or for longer intervals. It is in these cases that the change is most marked, and in one case was limited to the pyrexial periods and absent when the temperature was normal.* In the case of Group 2, on the other hand, I have failed to detect crystallisation even in cases of so-called cancerous cachexia when due to such tumours as scirrhus of the chest.

With regard to an explanation of these facts, we may at once assume that it is not by virtue of their malignancy alone—that is, by virtue of their being sarcomata or cancers—that these growths produce this result; for if a tumour composed of muscles or leucocytes had the same vascularity, the same rapidity of growth, it would probably produce the same effect. Further, the general volume of the blood seems to be affected, as we have seen, only in cases under Group 2, and in these only at a late period of the disease. The production of this blood change seems to be clearly connected in some way with the rapid cell growth and cell decay, the tissue change, and the increased metabolism which is going on at the site of the growth, and which produces its effect primarily on the blood circulating in the tumour. May not, in fact, the occasional elevation of temperature, alike with the crystalline degeneration of the red corpuscles, point to the liberation at this spot of some chemical product, the result of the rapid growth, decay, and death of these cell elements? Knowing, as we do, that blood left in contact with the tumour cells crystallises readily, even when a drop drawn from the general circulation shows no change, we may explain the absence of

* The whole subject of pyrexia in cases of malignant disease is one of great interest, and has not as yet been explained.

the crystalline change in slowly growing tumours and in many cases of malignant disease, on the supposition that, the breaking up and elimination of red corpuscles being active, the rapidity of growth and change at the site of the tumour is not sufficient to influence the whole volume of the blood. At all events, looked at from this standpoint, I think that a little light is thrown on the relation of the life of the tumour to the life of the individual, and on the influence of their rapid growth on the general nutrition, and the way in which they produce general blood change, anæmia, and death.

*Pyrexia due to Nerve Influence.*—No mention has yet been made of cases of high temperature due primarily to neurotic influence. Thus the blood has been examined in cases of marked pyrexia reaching 106° or 107° coming on suddenly after injury to the spinal cord high up in the neck; but this condition has been so transitory, the patients dying so soon, that I have not been surprised at the non-detection as yet of any crystalline change, especially when we bear in mind the probable absence in these cases of poisoning in the septic sense of the word. I have also failed to observe it in cases of rapid and transitory rises of temperature with rigors, following the passage of catheters, &c., when due to reflex irritation, and not absorption of septic matter.

*The Influence exercised by Local Conditions on the Blood in respect to this Crystalline Change.*—By local conditions are meant alterations in the tissues of any part of the body in which the blood circulates, such as a lowered vitality or death due to mechanical or chemical causes. We have already seen that blood from a case of splenic leucocythæmia, containing as it does such numbers of leucocytes, crystallises markedly; also that blood obtained from a rapidly growing sarcoma and left in contact with the sarcoma cells on a slide does so also, although blood drawn from the finger of the same patient does not crystallise. In like manner a drop of blood flowing from a puncture made in granulation tissue does not crystallise, while blood on a slide containing the teased-up granulation cells does so readily. The same holds

good for the spleen and liver. Now the question arises, How is this action on the red corpuscles brought about? Do the leucocytes, as they die and disintegrate, produce or liberate some ferment or chemical substance having this effect? Or do they simply act by depriving the hæmoglobin of the red corpuscles of its oxygen? And further, is the same influence exercised by damaged portions of any other tissues of the body as well as leucocytes and cell elements? The following observation may throw light here. The blood was examined from a calf's tail, and found not to crystallise. A ligature was then placed tightly around the lower end of the tail; the blood, thus rendered stagnant and in contact with the partially devitalised tissues, was examined at intervals of two and twelve hours and on the second day after, at which time the ligature was removed and necrosis had commenced; no crystallisation was detected except in one or two corpuscles on the second day. Also a drop of blood taken from tissues inflamed by mechanical means alone and unassociated with the presence of micro-organisms, as in eczema and burns of limited extent, does not crystallise, though this may be due to the fact that the individual corpuscles remain within the limited area of inflamed tissues for such a short time. Burns of large extent, in which there is a great reaction after the shock, especially in fatal cases, generally produce a general crystalline change in the whole volume of blood, even although suppuration has not yet occurred; this result may, however, be due to great congestion and interference with the large internal organs. On the whole, then, we may conclude that spleen pulp, leucocytes, and tumour cells, when injured by withdrawal from the body, exert some influence on blood in contact with them, leading to crystallisation of the hæmoglobin of the red corpuscles. Further, where great numbers of these cells or tissue elements live, degenerate, and die in the body, they produce the same change in the blood circulating amongst them, and in some cases this influence may be so great as to affect the whole volume of the blood, as in the case of rapidly growing malignant disease. The more highly

organised tissues, when injured, do not seem to exert the same influence either when in contact with blood on a slide outside the body or on blood circulating amongst them in the body. Extensive burns seem to be an exception, but we must in all these cases bear in mind the possibility of septic infection, which will of course produce the result.

As to the nature of this influence—whether, that is, these damaged leucocytes produce this crystallisation of the hæmoglobin by (1) the production or liberation by or from themselves of some chemical body or ferment, as in the case of coagulation; or (2) by depriving the red corpuscles of oxygen, or by both means combined, we do not yet know. As regards the manner of their action on a slide outside the body, it is interesting to note that the presence of mere organic foreign bodies, such as starch granules, in a drop of blood will not produce crystallisation, whereas the addition of some yeast fungus or torulæ brings about marked crystallisation, this fact suggests that the change in the blood is brought about by some action connected with the life of the leucocytes.

*The Influence of the Death of the Body on the Blood.*—Blood taken ten or twelve hours after death from the heart or large thoracic vessels of healthy persons who have died suddenly from accident almost always crystallises in about twenty-four hours; whereas blood taken from the vessels of the limbs crystallises but rarely, and then only after a long interval. Now we know that blood drawn during life and allowed to stand in a clean vessel does not crystallise even on a slide, at any rate in the case of man; and the difference in behaviour between the blood from the thorax and that from the limbs is probably due to the fact that the blood in the large cavities is kept warm for some hours after death, and within easy reach of the septic-gas containing hollow abdominal viscera. Moreover, the fluids in these cavities, thorax and abdomen, undergo a rapid change of some kind after death; for though normal pericardial fluid, when added to a drop of normal blood on a slide, produces no change, pericardial

fluid taken from a healthy man twelve hours after death, and added to a drop of normal blood, produces marked crystallisation, although no organism can be detected in the fluid at the time. Further, the condition of the patient at the time of death also makes a great difference. Thus the blood of persons dying from wasting and febrile diseases, even though not crystallising during life, does so after death much more quickly and readily than the blood of healthy persons dying suddenly.

*Crystallisation in Animals.*—The tendency to crystallisation of the hæmoglobin in different animals of course varies greatly, not only in health and when treated by the many and well-known methods and reagents, but also in disease and when observed after the method explained above. Thus, in the mouse, wild and tame, at one end of the series, crystallisation readily occurs in the unaltered drop of blood on a slide, as explained above; in the field mouse it does so more slowly and less fully, also in the rat; and in the hedgehog, mole, guinea-pig, and rabbit it occurs with great difficulty when treated thus, though easily obtainable from these animals by treating the blood with reagents. In the dog there is no crystallisation in health; and in the cat there is slight crystallisation in a few corpuscles from the general circulation; it is, however, well marked in blood taken from the splenic vein during life, and less so in the hepatic vein; the animal, however, was dying from chloroform poisoning by inhalation; but this excess of crystallisation in the splenic vein points again to the influence of the spleen pulp on the red corpuscles circulating in it. The larger domestic animals seem to resemble man in the matter of crystallisation. Thus, in the sheep, though absent in health, I have detected the change in the blood of "rotten" sheep, also in cases of uterine inflammation after lambing, and in cases of the peculiar wasting affection found on cold undrained lands attended with destructive joint changes; on the other hand, it was absent in a lamb and sheep both dying suddenly from pericardial effusion or "red water." Although the crystals of hæmoglobin appear-

ing thus spontaneously, as it were, in the blood, belong in different animals, with few exceptions, to the same system, yet in these different species they present tendencies to assume for the most part one shape or size peculiar to that species or animal. Thus, in the sheep, in addition to the needles, the plates are generally of a diamond shape, unlike those of man. This points to a considerable difference in the intimate constitution of the hæmoglobin of various animals—a subject well worthy of further investigation. In the case of a wild mouse caught near Wimbledon in 1880, in which numerous actively moving flagellate organisms, probably identical with those described by Lewis as occurring in the rat, were found in the blood, very slight crystallisation was detected—less, in fact, than usual; thus giving another example, as was suggested in the case of anthrax, of an affection in which the parasite kills the host by the mechanical invasion of its fluids and tissues, rather than by the production or liberation of any chemical product. I have not detected any crystallisation in the nucleated corpuscles of toads, newts, or birds; in the fish, however (roach), it occurs readily, in health, in the form of needles and diamond plates. Thus, though animals differ in the tendency to crystallisation during health and in the unaltered blood, they resemble man in this respect, that in diseases of a septic nature and in others, and in the case, too, of blood to which septic serum has been added on a slide outside the body, crystallisation generally occurs.

What is the nature of this change shown by the hæmoglobin under these peculiar conditions? Whether we regard the blood according to the older views as an albuminous fluid only, in which float the corpuscular bodies, red and white, or whether we regard it in the new light suggested by Wooldridge and others, and consider it as a sort of embryonic tissue, an undifferentiated fluid protoplasm, in which the red corpuscles arise, or are born, as it were, by the differentiation and coloration of the little portions of protoplasm forming each corpuscle,—whichever view we take, we are

here concerned only with the ultimate composition of the blood, and simply regard it as composed of an albuminous fluid portion or plasma, and a more solid or corpuscular portion, each corpuscle of which consists of a protoplasmic stroma containing in loose combination, or in some sort of physico-chemical association, a proteid-coloured body called hæmoglobin. This body is capable of existing in a crystalline and in a colloidal form, and in an oxydised and in a reduced condition, and it is now for us to attempt to explain the occurrence of the crystalline form in the blood of man in disease, since it only exists during health in the colloidal state. As regards the real nature of this change, we know that it is not due to a mere alteration of plasma or corpuscles due to high temperature, for it is absent in rheumatic fever. Neither is it owing to a disturbance of the relation between solid and fluid constituents, for it is not found in the blood of persons extremely anæmic from severe hæmorrhage. Neither is it simply a diminution in the volume or amount of the hæmoglobin, for it is absent in chlorosis. Now it happens that the result obtained by the disease—for instance, septicæmia—on the blood within the body can be produced by the addition to a drop of normal blood on a slide outside the body of some of the poison producing the disease. Thus, if a drop of putrefactive human serum be added to a drop of normal blood on a slide, well-marked crystallisation of the hæmoglobin occurs in twenty-four hours. And this holds good of other diseases, care being of course always taken to use only serum as the vehicle of the poison, so as to alter the composition of the blood as little as possible. In this way various agents can be used and the nature of the change more easily investigated. If a specimen of blood in which this change is going on be watched under a cover glass, it will be found that the first change, occurring in from six to eighteen hours, is nearly always an exudation more or less of the hæmoglobin into the serum; the corpuscles grow pale, while the serum assumes a yellowish tinge. A little later, in from twelve to twenty-four hours, it will be found that crystallisation has

occurred, and this chiefly in the red corpuscles, and, if the exudation of hæmoglobin has been marked, in the dissolved hæmoglobin also, around the margin, not, however, the extreme edge, of the cover glass. If normal blood be allowed to stand in quantity to which some hydrocele fluid which has been exposed to the air for some days is added, crystallisation does not occur to any extent in the blood standing in mass, but it appears as soon as a drop of such septicised blood is tranferred to a slide and allowed to remain twenty-four hours; and if some of the same hydrocele fluid be added to a drop of fresh blood on a slide, crystallisation also occurs in twenty-four hours; whereas, fresh hydrocle fluid, free from organisms or their products, has no power to produce this change. From this it appears that the change brought about by the poison in the first instance, is an increased exudation of the hæmoglobin out of the corpuscles into the plasma, and then, when the conditions are favourable as to evaporation, &c., as on a slide, crystallisation occurs in the exuded hæmoglobin and also in the corpuscles, the crystallisation being the second term in the series of changes. But this crystallisation is not merely an accident due to the exudation of the hæmoglobin and subsequent evaporation of the serum. This is proved by the fact that it is absent in the blood of typhoid fever patients, although in this disease there is considerable exudation of the hæmoglobin, and the conditions favouring evaporation are the same. And further, in many cases where the poison is highly concentrated, crystallisation occurs within the red corpuscles, before exudation of the hæmoglobin can occur. Thus the first effect of the poison in a moderate dose is to produce exudation of hæmoglobin, and, secondly, the conversion of this body from the colloid to the crystalline condition.

Now, bearing in mind that, though soluble in serum, the hæmoglobin does not leave the red corpuscles under normal conditions and in health, and since mere alteration of the density, &c., of the serum alone has no power to bring about crystallisation, we are led to think that the action of the

poison falls chiefly on the red corpuscles, and consists in a lowering of the vitality of the stroma, rendering it incapable of retaining the hæmoglobin in association with itself, just as in order to prepare hæmoglobin artificially, it is necessary to destroy the stroma by reagents, or by repeated freezing and thawing. Further, this hæmoglobin, being itself a highly complex substance composed of a proteid body (globulin) and a coloured compound (hæmatin), is probably also affected itself; its vitality is also reduced, for it is converted from the semi-fluid colloidal state in which it exists in association with the stroma into the rigid, less vitalised, crystallised state.* But this is not all. If a drop of normal blood be watched on a slide for some days, it will, on examination with the micro-spectroscope, always show the two narrow bands characteristic of oxyhæmoglobin; it becomes—remains, in fact, in an oxygenated or arterial condition, even though venous or deoxidised when first drawn. On the other hand, in poisoned or crystallisable blood, one of the first changes after the exudation of the hæmoglobin is that, no matter in what state it was when first placed on the slide, it invariably shows the one broad band characteristic of reduced hæmoglobin; it becomes, in fact, very venous in proportion as the exudation and crystalline changes progress. This reduced spectrum is not obtained at first alike all over the field, but occurs first in patches where the exudation and crystallisation are setting in—not, however, just round the extreme margin of the cover glass, for here, just inside the dried blood, which forms a protecting scab, is a zone of highly oxygenated blood, in which neither exudation nor crystallisation ever takes place. The crystalline and venous changes occur in a wide zone just inside this oxygenated zone, and this relation of zones is, no doubt, determined by the physical conditions of exposure, evaporation, &c., the important point being, that these changes do not occur in blood which is not diseased, or has not been treated with septic serum in the way described.

* The crystallisation in fact appears to be a sort of "rigor mortis" of the red corpuscles.

Further, although the crystals of hæmoglobin, when obtained by the usual method, are capable of existing in the oxidised or in the reduced condition, yet when occurring in such poisoned blood, they are, like the blood, always in the reduced or venous state; this is shown both by their purple colour and by the micro-spectroscope.

Now, this fact—namely, that the hæmoglobin of patients suffering from these diseases, septic and others in which crystallisation occurs when placed on a slide, always loses its oyxgen, whereas the hæmoglobin of normal blood, when so treated, always gains or retains its oxygen, no matter in what state it is when drawn—is very important. Such hæmoglobin has not lost the power to take up oxygen, for when exposed to the air the blood again becomes arterial, but when confined under the cover glass and the air excluded by the dried scab, it in some manner has the oxygen removed from it. Now the question is, What is the agent by which this loss of oxygen is brought about? Mere organic foreign bodies, such as starch granules, do not produce either exudation, crystallisation, or reduction of the hæmoglobin. If, on the other hand, some living torulæ cerevisiæ be added, then deoxidation occurs in addition to the exudation and crystallisation described above. Torulæ differ from starch granules, especially in these particulars—that they are alive, that they are associated under certain conditions with fermentative changes, and that they require and abstract oxygen from the surrounding media. Moreover, we have seen above that the contact of leucocytes or sarcoma cells with the blood under like conditions will bring about this exudation, crystallisation, and deoxidation, and there is evidence to show that leucocytes and bodies resembling them, in addition to requiring oxygen, are associated, when injured or undergoing disintegration, with some ferment-like bodies, having important effects on the blood as regards its tendency to crystallisation.

Judging, then, from the foregoing facts, I may state that the blood in the septic and infective diseases mentioned

above, also when associated with the presence of large quantities of leucocytes or sarcoma cells and cell elements of a like nature, or when treated outside the body by the addition of septic serum, undergoes certain changes in which the hæmoglobin especially suffers—passing through a triple retrogressive change of exudation into the serum, deoxidisation, and crystallisation. Though, of course, it is extremely difficult to separate and distinguish between effects due to the mere presence of the micro-organism, and those due to the products of the growth, yet we know that in some affections, at any rate such as sapræmia, the change in the hæmoglobin is associated with the presence in the blood of certain chemical products, the micro-organisms themselves not getting into the circulation. From these and other facts we are led to believe that it is the chemical albuminous ferment-like bodies which are produced by the growth of the organisms in the one case, and the products of the disintegration of the devitalised leucocytes or tumour cells in the other, which brings about these changes in the hæmoglobin, and not the mere presence of the organisms or leucocytes themselves.

I am fully aware that there are many cases in which a further examination of the blood may throw important light. Thus it would be especially interesting to note the presence or absence of this change in the case of poisoning by snake bite, the poison of which has now been more fully worked out; also the injection of the isolated products—such as sepsin, &c.—themselves into the circulation, would give additional evidence; also the injection of bodies of an analogous nature—such as the ferments, pepsin, trypsin, &c. For these and other experiments, further opportunities may arise.

In conclusion, I venture to think that the results obtained and stated in the foregoing pages explain certain phenomena which have hitherto existed as isolated facts. It has been known for some time that the actual quantity of oxygen in the arterial blood of animals suffering from septic disease is diminished; this is now explained by the deoxidising action

of the poison on the hæmoglobin. It is also of course frequently observed that considerable post-mortem blood staining of the endocardium and interior of the large vessels occurs in the bodies of patients dying from septic diseases. We have seen above how the action of the poison of these diseases is to cause exudation of the hæmoglobin from the red corpuscles into the serum, and so to bring it in contact with the tissues.

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